Public Health Emergencies: 
Use of Real-time Mobile Communications

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NATIONAL PUBLIC HEALTH EMERGENCY PREPAREDNESS:

2009 H1N1 INFLUENZA A PANDEMIC

www.fda.gov
2009 H1N1 Influenza Pandemic

A novel flu strain evolved from a combination of genetic elements from avian, pig, and human virus strains.

US Secretary of DHHS declared a public health emergency on April 26, 2009.

WHO declared a global pandemic on June 11, 2009.

By end of August 2009, cases reported in >180 countries.
2009 H1N1 Influenza A Pandemic in the US

FDA Commissioner issues an EUA for peramivir on October 23, 2009.

An EUA:

1. May be issued by FDA Commissioner based on HHS Secretary declaration of an emergency or threat of an emergency.

2. Allows FDA to facilitate availability and unapproved use of MCMs to prepare for and respond to CBRN emergencies.

3. Authorizes access to a drug or device subject to specified conditions.

4. Is not considered a clinical trial of an unapproved drug or device.

5. May include unapproved products or approved products intended for unapproved use(s).

Medical countermeasures (MCM) refer to drugs, biologic products, antidotes, vaccines, in vitro diagnostic laboratory tests, and other drug products or devices.

CBRN = chemical, biological, radiological, or nuclear, including emerging infectious diseases (pandemic influenza)
An **EUA** is separate from medical product use under investigational new drug application (IND) or investigational device exemption (IDE).

### Criteria for Emergency Use Authorizations (EUAs), Investigational New Drug Applications (INDs), Emergency Investigational New Drug Applications (EINDS), and FDA-Approved Prescription Products.

<table>
<thead>
<tr>
<th>EUA, in General (and for Peramivir)</th>
<th>EIND</th>
<th>IND</th>
<th>FDA-Approved Prescription Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad or restricted according to the letter of authorization (peramivir: seriously ill, hospitalized patients)</td>
<td>Single patient with serious illness or immediately life-threatening condition</td>
<td>Limited to clinical trials or expanded access</td>
<td>By prescription</td>
</tr>
<tr>
<td>Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to the conditions of authorization (peramivir: intravenous administration in a hospital)</td>
<td>Limited to single patient</td>
<td>Limited to clinical trials or expanded access</td>
<td>According to labeling and practice of medicine</td>
</tr>
<tr>
<td>Efficacy requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasonable to believe based on totality of scientific evidence, including adequate and well-controlled trials as available (peramivir: benefit observed in patients with acute, uncomplicated influenza)</td>
<td>Rationale for intended use, risk from treatment should be no greater than risk from disease or condition</td>
<td>No efficacy requirements, but safety data from animal studies are needed</td>
<td>Substantial evidence based on adequate and well-controlled clinical trials</td>
</tr>
<tr>
<td>Prescriber safety reporting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to the conditions of authorization (peramivir: mandatory)</td>
<td>Required per IND regulations</td>
<td>Required per IND regulations</td>
<td>Voluntary MedWatch reporting</td>
</tr>
<tr>
<td>Informed consent</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Approval by institutional review board</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
FDA Adverse Event Reporting System (FAERS)

FDA Form 3500 (MedWatch)
The EUA for intravenous peramivir in October 2009 was the first EUA authorized for an unapproved drug product in the US.

The MedWatch reports served as the primary source of safety information for FDA.

MedWatch reporting was subject to underreporting and missing data. The data was confounded in some instances by severity of influenza, concomitant drugs, and concurrent medical disorders.
Lessons learned: pandemic preparedness

- **MedWatch reports were time consuming** for reporters, and analysis was limited by **variable quality of reporting and missing data**
- **Need for systems to handle real-time reporting** of safety concerns, changes in clinical condition, and patient outcomes
- **Limited technical tools** to extract, analyze, and share information in real-time for surveillance and decision making purposes
- **Need for a dedicated data management platform** for integrating and analyzing information from multiple data streams
- **Need for real-time bidirectional communication** during a declared national emergency to foster communication and information sharing
Real Time Application for Portable Interactive Devices

Henry Francis, M.D.
FDA/CDER/OTS
• RAPID is the FDA’s first bidirectional communication system.
• Mobile applications for data collection
• Data lake to store diverse data resources, including information on adverse drug reactions, and analytics to enable FDA to detect emerging drug safety signals
• Changes how FDA will conduct post-market product surveillance
• Enhances emergency preparedness and response involving medical countermeasures (MCM)
FDA requires a real-time active surveillance application to support pharmacovigilance and adverse event reporting in MCM situation

The Solution

- Real-time Application for Portable Interactive Device (RAPID) will facilitate the real-time collection, analysis, and communication of MCM product and health information during national public health emergencies
- Flexible Mobile platform to use during MCM events
- Flexible FDA cloud design complementary to FAERS
- Adaptable data management and analysis system
- Bidirectional CDER multimedia communications
- Decision maker data work bench
Dear Dr. Teller,

Thank you for your recent adverse event submission. We would like to provide you with additional information about the adverse event report you submitted. Please use the link or QR code below to access and share this information.

https://fda.gov/peramivirpodcase880

Thank you,
FDA
RAPID

• Organized in four tiers:
  – Mobile app for collection of incoming diverse information
  – A data lake to store diverse data resources, including information on adverse drug reactions, and analytics to enable FDA to detect emerging drug safety signals
  – Data visualization dashboards to assess patterns in data and allow emerging issues to be explored
  – Presents information and analyses to leadership to support decision making and guidance to ensure patient safety
The cloud-based RAPID Bio-surveillance System will support collaboration between FDA and other Federal agencies to enhance monitoring emerging health threats.

**RAPID Biosurveillance System**

**Tier 1: Regulatory Action/Guidance**
- FDA and external partners issue guidance to ensure patient safety

**Tier 2: Data Visualization**
- Dashboards summarizing key information provide safety alerts
- Disproportionality metrics and detailed analyses allow FDA and collaborators to understand emerging issues

**Tier 3: Data Management & Analytics**
- RAPID data is combined with existing MedWatch and Medwatcher reports and data from external collaborators
- Advanced analytics support AE signal detection

**Tier 4: Processing of Adverse Events**
- Healthcare professionals submit AE data via the RAPID mobile app
- AE data is stored in a “data lake” to support real-time access
Tier 4 of the cloud-based RAPID Biosurveillance System includes the processing of adverse events submitted by clinicians, healthcare professionals and other reporters.

- Healthcare professionals submit AE data via the RAPID mobile app.
- AE data is stored in a “data lake” to support real-time access.
Tier 3 of the cloud-based RAPID Biosurveillance System includes data storage, data integration, and advanced analytics to support adverse event signal detection.

**RAPID Biosurveillance System**

**Tier 3: Data Management & Analytics**
- RAPID data is combined with existing MedWatch reports and data from external collaborators
- Advanced analytics support AE signal detection
Tier 2 of the cloud-based RAPID Biosurveillance System includes visualization of adverse event trends for interpretation by FDA staff and external collaborators.

**RAPID Biosurveillance System**

**Tier 2: Data Visualization**
- Dashboards summarizing key information provide safety alerts
- Disproportionality metrics and detailed analyses allow FDA and collaborators to understand emerging issues
The cloud-based RAPID Biosurveillance System will support collaboration between FDA and other Federal agencies to enhance monitoring of investigational therapies for Ebola and other emerging health threats.

**RAPID Biosurveillance System**

**Tier 1: Regulatory Action/Guidance**
- FDA and external partners issue guidance to ensure patient safety
FDA collaborators in MCM events

- Federal agencies
- Healthcare providers
- Healthcare facilities
- Individuals
- Sponsors
RAPID use cases

• Non-MCM
  – Product Safety Surveillance
  – Risk Evaluation and Mitigation Strategies (REMS)
  – Medication Errors

• MCM related
  – Real time patient outcome and safety data collection
  – Streaming data
  – Merging data resources, e.g. weather and disease patterns

MCM = medical countermeasures
• Cloud-based storage in a data lake (can accommodate streaming information while minimizing need for physical servers)
• Analytics dashboard, including geolocation functionalities
• Secure data broker to allow approved outside collaborators to view mirrored information
DPV - Adverse Event Report Use Case

1. Healthcare Professionals and consumers submit regular and emergency surveillance adverse event reports

2. General Surveillance
   - Mobile Data Collection: Clinicians, reporters, and patients create general surveillance and emergency surveillance reports
   - Data Transferred to FDA: Data is submitted from mobile device and sent over Cellular network or WiFi to FDA GovCloud via web services
   - Perform Analytics: Utilize RAPID Dashboard, location based data, and Empirica (signal detection) for analysis
   - Response Sent to Reporter: Within 24 hours a targeted response is sent via email containing links to multimedia files like images and podcasts

3. RAPID External Data (Future)
   - Obtain External Data: Data will be shared from external sources via web services (ex. HL7 ICSR) and increase the effectiveness of analysis performed using RAPID analytical tools

4. AWS GovCloud

5. RAPID Heatmap
   - Empirica

Adverse Event Analytical Tools
- RAPID AE Dashboard & Data
- Geovisualization
Dashboard: Homepage for Regulatory Review

**Search the RAPID database**

Filter the list of adverse event reports shown in the dashboard.

- **Product Name**
- **MedDRA terms**
  - All PT
  - Angioedema
  - Aplastic anaemia
  - Delirium
  - Diarrhoea

**Results by Adverse Event Outcomes**

- **Disability or Permanent Damage**
- **Death**
- **Life-threatening**
- **Congenital Anomaly/Birth Defect**
- **Hospitalization - Initial or Prolonged**
- **Other Serious (Important Medical Events)**
- **Required Intervention to Prevent Permanent Impairment/Damage (Devices)**
- **Non-Serious**

**Recent Submissions**

120 cases submitted for PERAMIVIR since 05/15/2014

<table>
<thead>
<tr>
<th>Case #</th>
<th>Suspect Product Name</th>
<th>Adverse Event Outcomes</th>
<th>PT</th>
<th>Submit Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>35241</td>
<td>PERAMIVIR</td>
<td>Non-Serious</td>
<td>Headache</td>
<td>12/03/2015</td>
</tr>
<tr>
<td>35241</td>
<td>PERAMIVIR</td>
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**Map View**

Past Year
RAPID GIS Visualizing Functionality

[Image of a map showing data points with a window overlay displaying specific outcomes and details]

Outcomes Dashboard: PERAMIVIR
(Case #: 659)

Case Number: 659
Product: PERAMIVIR
Adverse Event (AE) Outcome: Death
Adverse Event (AE) Terms:
Delirium, Aneutropenia, Pancreatitis, Sinus Bradycardia
Age: [Details]
Gender: MALE
Adverse Event (AE) Start Date: 02-FEB-14
Adverse Event (AE) End Date: [Details]
Report Submit Date: 04-FEB-2014
**DRISK - REMS Assessment Use Case**

1. **Mobile Data Collection:**
   Prescribers, pharmacists, and patients complete the REMS Assessment using the RAPID app on their mobile device.

2. **Data Transferred to FDA:**
   Data is submitted from mobile device and sent over Cellular network or WiFi to GovCloud via web services.

3. **Perform Analytics:**
   Utilize the REMS Dashboard to view composite scores, results by domain, and to perform additional analysis.

4. **Response Sent to Reporter:**
   Send email containing information about the REMS Program back to the user.
**DMEPA – Medication Error Use Case**

1. **Mobile Data Collection:**
   Prescriber completes a Medication Error Report and attaches an image using the RAPID app on their mobile device.

2. **Data Transferred to FDA:**
   Data is submitted from mobile device and sent over Cellular network or WiFi to GovCloud via web services.

3. **Perform Analytics:**
   Utilize the Medication Error Dashboard to view overview of the medication error reports that are being submitted.

4. **Response Sent to Reporter:**
   Send email containing information about the Medication Error back to the user.
RAPID Dashboard for Agency Leadership
• Designed to streamline completion of FDA Form 3500A (MedWatch) more efficiently and in less time (from approximately 45 minutes to 5 minutes)
• Includes voice-recognition technology to capture dictated response information
• Captures pictures, small videos, and other image recordings taken with mobile phones
• Provides bi-directional communication functionality so that FDA can send back information (such as how to use the drug and potential side effects to be aware of)
The Real-time Application for Portable Interactive Devices (RAPID) System can inform decision-making at the physician, hospital and Federal level.

### Data from RAPID combined with other systems

**ASPR – RAPID enables improved management of MCM stockpiles**
- Number and location of stockpiles (drugs, vaccines, diagnostics)
- Type, severity and location of potential CBRN threats
- Syndromic surveillance data from state/local public health agencies

**Hospital Administrators – RAPID supports allocation of healthcare resources**
- Number of occupied beds
- Patient characteristics (diagnoses, level of care, etc.)
- Patient status (waiting for treatment, ready for hospital discharge, etc.)

**Physicians – RAPID informs diagnosis and treatment of patients**
- Patient history data
- Physical exam data
- Laboratory data
- Medical equipment data (diagnostic, treatment, life support, monitors, etc.)

### Key questions and capabilities that can be addressed with RAPID data

**Monthly**
- How to manage stockpile inventory and location?
- How to get MCM resources to patients and at-risk populations?
- What types of threats are most likely to occur in the short- and long-term?

**Daily**
- How to manage current patient flow?
- How many patients are projected to require care in the short- & long-term?
- What number and type of medical equipment are required to diagnose and treat patients in short- & long-term?

**Streaming**
- How to diagnose the patient based on symptoms, history, and data from others?
- How can data from other patients influence the current patient’s treatment plan?
- What drugs, vaccines and/or diagnostics should be ordered to treat the patient?

**RAPID Secure Data Broker (SDB) – Provides access to adverse event reports and electronic health records to inform decisions made by physicians, hospitals and the Assistant Secretary.**

**RAPID Mobile Application**

**Clinical Decision Support**

**Hospital Alerts**

**Geographic visualizations**
The proposed RAPID Biosurveillance Platform includes a cloud-based open source big data analytic tool to facilitate the detection of adverse event signals in near real-time.

Additional data sources can be integrated to augment product safety information received via the RAPID mobile application.

### Alerts ...

<table>
<thead>
<tr>
<th>Drug Event Tracker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Peramivir-H1N1</td>
</tr>
<tr>
<td>Avandia- Diabetes</td>
</tr>
<tr>
<td>MPA-Steroid Injections</td>
</tr>
<tr>
<td>Zanamivir- H1N1</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
</tr>
</tbody>
</table>

1) **Alerts**: Display drugs with > 50% increase in the number of reports in the last 2 weeks
2) **Drug-AE Filter**: Show drugs with AEs linked to fatal outcomes or pediatric populations
3) **Disproportionality Metric Filter**: Show ROR, PRR and other disproportionality metrics

### Time Series Visualization for Number of Reports for Drug of Interest: Adverse Event Data and Social Media Data

*Mouseover or use the arrow keys to inspect values*

*Mouseover bubbles to view information on adverse events reported at different geographic locations*
Drug Safety Surveillance, Data Mining, and Data Analytics
Diverse Biomedical Resources for Drug and Biologic Product Safety Surveillance

Pharmacovigilance Data Sources

- Health Records
- Spontaneous Reports
- Biomedical Literature
- Clinical Trials
- Administrative claims data
- Chemical & Biological
- Social Media
- Search Logs
- Product Labeling

FAERS
FDA Adverse Event Reporting System

MEDLINE

Sentinel Initiative

ClinicalTrials.gov

DAILYMED

FDA
FDA Adverse Event Reporting System (FAERS)

- Centralized repository of postmarket spontaneous adverse event reports submitted by manufacturers and consumers
- Human drugs and therapeutic biologic products
- >9 million reports since 1969
- Approximately 1.5 million reports /year
- Detection of rare ADEs not observed in clinical trials
• Bibliographic database of more than 26 million biomedical citations

• Developed a novel prototype web-based tool (PEARL) that leverages Medical Subject Heading (MeSH) indexing terms to extract citations reporting adverse drug events (ADEs)
  – We used combinations of MeSH descriptors (and supplementary concepts) and qualifiers to identify drugs involved in ADEs (e.g., ofloxacin/adverse effects) and clinical manifestations reflecting an ADE (e.g., tendinopathy/chemically induced).

• Explored various statistical approaches for data mining to detect emerging ADE safety signals
PEARL web-based analytical tool

► First-of-its-kind information technology tool

► Builds capacity to harness biomedical resources to support pre- and post-market regulatory decisions

► Complementary to existing resources (e.g., FAERS)
**PEARL** Web-based analytical tool:
Featured visualizations

**Top 10 Adverse Drug Events**

**Exportable Data Mining Outputs**

**Tree Maps**

**Heat Maps**

**Drug Class Level**

**Time Course Graph**
PEARL detects drug-adverse event safety signals from diverse scientific literature
Weekly PubMed Literature ‘Alerts’

- Aim: to detect safety and efficacy issues that are newly emerging and not known prior to the search
- Leverages existing search functionality in PubMed (MyNCBI)
- Focus on the most recently deposited PubMed/MEDLINE citations that have not yet been MeSH indexed

**Featured Functionalities**

Managed customized literature search queries

**My NCBI**

- Search NCBI databases
- Saved Searches
- My Bibliography
- Recent Activity

**Sample literature ‘Alert’ email**

Advisers say FDA’s opioid REMS program needs improvement.
• A registry and database of clinical trials established as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA).
• Expanded in 2007 under the Food and Drug Administration Amendments Act (FDAAA) to require the reporting of summary results, including adverse events, for certain trials
A total of 22,546 completed studies with results through June 2017.
Electronic Health Records

- Preliminary work designed to establish a block chain-mediated connection between a group of selected USCIIT participating hospitals and FDA
- Identify influenza cases using patient level data for case reporting and patient outcome evaluation
- Ensure removal or anonymize PII/PHI data
- Use FHIR accelerator to onboard hospitals
- Operations and analytics to be conducted in secure data broker and FDA GovCloud

PII = personally identifiable information; PHI = protected health information
USCIIT = US Critical Illness and Injury Trials Group
RAPID Summary

• Bidirectional mobile platform to collect information and analyze it in real-time, and provide information/response back within 24 hours
• Enhance efficiency and speed of response to urgent public health needs
• Flexible data and analytic cloud platform
• Enhances product safety surveillance activities
• Use cases oriented to medical countermeasures in response to emerging infectious disease threats (pandemic influenza), CBRN agents, REMS, and medication errors

CBRN = chemical, biological, radiological, or nuclear;
REMS = risk evaluation and mitigation strategy